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Cancer. 2015 May 15; 121(10): 1681–1687. doi:10.1002/cncr.29216.**Teenage acne and cancer risk in U.S. women: A prospective cohort study****Mingfeng Zhang, MD, PhD¹, Abrar A. Qureshi, MD, MPH², Renée T. Fortner, PhD³, Susan E. Hankinson, ScD^{3,4}, Qingyi Wei, MD, PhD⁵, Li-E Wang, MD, M.Sc.⁶, A. Heather Eliassen, ScD^{3,7}, Walter C. Willett, MD, Dr.P.H.^{3,7,8}, David J. Hunter, ScD^{3,7,8}, and Jiali Han, PhD^{9,10,11,*}**¹Department of Dermatology, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA²Department of Dermatology, Rhode Island Hospital, Warren Alpert Medical School, Brown University, Providence, RI, USA³Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA⁴Department of Public Health, School of Public Health and Health Sciences, University of Massachusetts Amherst, MA, USA⁵Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA⁶Department of Epidemiology, the University of Texas M.D. Anderson Cancer Center, Houston, TX, USA⁷Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA⁸Department of Nutrition, Harvard School of Public Health, Boston, MA, USA⁹Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN, USA¹⁰Melvin and Bren Simon Cancer Center, Indiana University, Indianapolis, IN, USA¹¹Department of Dermatology, School of Medicine, Indiana University, Indianapolis, IN, USA**Abstract**

Background—Acne reflects hormone imbalance and is a key component of several systemic diseases. We hypothesized that diagnosis of acne at teenage might predict subsequent risk of hormone-related cancers.

Methods—We followed 99,128 female nurses for 20 years (1989-2009) in the Nurses' Health Study II cohort and used Cox proportional hazards models to estimate the hazard ratios (HRs) of

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None declared.

eight specific cancers (breast, thyroid, colorectal, ovarian, cervical, endometrial cancers, melanoma and non-Hodgkin's lymphoma) for women with a history of severe teenage acne.

Results—After thoroughly adjusted for the previously known risk factors of each cancer, we found that among women with a history of severe teenage acne, the relative risk increased with multivariable-adjusted HR of 1.44 (95% confidence interval [CI], 1.03-2.01) for melanoma. We replicated this association in an independent case-control study of 930 cases and 1,026 controls (multivariable-adjusted odds ratio, OR, 1.27; 95% CI, 1.03-1.56). We additionally found that the individuals with teenage acne were more likely to have moles in both studies (52.7% vs. 50.1%, $P<0.001$ in the cohort study; and 55.2% vs. 45.1%, $P=0.004$ in the case-control study).

Conclusion—Our findings suggest that a history of teenage acne might be a novel risk factor for melanoma independently from the known factors, which supports a need for continued investigation of these relationships.

Keywords

Acne; Cancer; Melanoma; Mole; Telomere length; Androgen

Introduction

Acne vulgaris, one of the most prevalent skin conditions and the leading diagnosis in dermatology, affects more than 85% of teenagers¹. It is a follicular phenotype characterized by the hyperplasia of the sebaceous glands and seborrhea. Several hormones have been linked to acne, including androgens, estrogens, growth hormone, insulin, adrenocorticotrophic hormone, melanocortins, *et al.*². Among them, androgens, the male hormones present in both men and women, have long been known to contribute to acne flares by over-stimulating the oil glands and altering the development of skin cells that line hair follicles in the skin.

Cancer is a systemic disease and a number of major cancers are hormone-related³. Compelling evidence has implicated estrogens in the etiology of breast cancer, progesterone in the etiology of breast and ovary cancers, and testosterone in the etiology of prostate cancer⁴. Besides, estrogens have been suggested to play a role in many other major cancers, including endometrial, ovary, esophageal, colorectal, cervical, thyroid and lung cancers, melanoma and non-Hodgkin's lymphoma⁵. The hormonal effect of testosterone has been suggested in breast⁴, ovary⁶, endometrial⁷, colorectal⁸ cancers and melanoma⁹. Thus, it is plausible that acne may be a predictor of cancer risk. It has been suggested that men with severe acne had an elevated risk of prostate cancer in the Health Professionals' Follow-up Study¹⁰. However, the association between acne and breast cancer risk has been inconclusive, with positive, inverse and null association results¹¹⁻¹⁴. To prospectively investigate the association between teenage acne and cancer risk in women, we conducted a prospective analysis in the Nurses' Health Study II (NHSII), with 116,430 women followed up for over 20 years in the U.S.

Materials and Methods

History of severe teenage acne and cancer risk in the NHSII

Study population—The NHSII is a prospective cohort study established in 1989, when 116,430 female registered nurses aged 25-42 completed an initial questionnaire on their medical histories and health-related exposures. Updated information was obtained by mailed questionnaires biennially. Details of this cohort have been described previously¹⁵. The protocol for this study was approved by the Institutional Review Board at Brigham and Women's Hospital and the Harvard School of Public Health. Informed consent was obtained from the cohort participants.

Exposure data—Participants reported their history of severe teenage acne on the baseline questionnaire in 1989. We collected information on the use of medications for acne treatment, including tetracycline and oral isotretinoin (brand name: Accutane) in 1993, and the use of antibiotics for acne in 2005. Details on the data of other potential cancer risk factors were described in the Supplementary Methods.

Identification of cancer cases—Participants reported cancer diagnoses biennially. With their permission, pathological records were obtained and reviewed by physicians to confirm diagnosis. Eligible cases consisted of women with incident cancers diagnosed any time after the baseline up to the 2009 follow-up cycle. Only pathologically confirmed invasive cases were included, except for breast cancer, which included both invasive (n=2,640) and *in situ* (n=663) cases. We included eight specific cancer sites in which the hormonal effects were previously implicated and of which there were more than 100 cases. We additionally examined non-melanoma skin cancers as a comparison to assess the potential confounders of skin cancer risk such as ultraviolet exposure and dermatology clinic visit. Medical records were not obtained for self-reported cases of basal cell carcinoma (BCC), but previous reports have demonstrated the high validity of self-report of BCC, with more than 90% confirmed by histopathology records in the NHS¹⁶.

Melanoma case-control study from the MD Anderson Cancer Center

Between April 1994 and April 2008, 930 patients with newly diagnosed, histologically confirmed, untreated cutaneous malignant melanoma and 1,026 matched controls were consecutively recruited at the MD Anderson Cancer Center. With informed consent, we collected information about history of teenage acne as well as demographic and known risk factors for melanoma for each patient. We only included U.S. non-Hispanic Europeans in this analysis. Details of the study population have previously been described¹⁷. The research protocol was approved by the Institutional Review Board at the MD Anderson Cancer Center.

Plasma Hormone Study

Between 1996 and 1999, a subgroup of NHSII provided plasma samples (n=29,611)^{18; 19}. Details of the collection were described in the Supplementary Methods. Women who had data for testosterone, sex hormone-binding globulin (SHBG) or dehydroepiandrosterone sulfate (DHEAS), and did not report treatments for acne were included. Free testosterone

was calculated using the method described by Sodergard *et al.*²⁰. We selected plasma testosterone and DHEAS given their associations with breast cancer risk in the NHSII^{18; 19}. Free testosterone is the biologically active form of testosterone and DHEAS is the primary circulating form of DHEA.

Statistical Analysis

Participants contributed person-time from the baseline in June 1989 to the end of follow-up in June 2009. A total of 99,128 women were included in this study at the baseline after excluding those with previous cancers or missing information on the history of severe teenage acne. Accumulation of follow-up time ceased at the first report (followed by confirmation) of a primary cancer, death, or the end of follow-up, whichever came earlier. We adjusted for the previously known risk factors for each cancer in the multivariable Cox proportional hazards models and calculate the hazard ratios (HRs) and 95% confidence intervals (CIs)²¹. We calculated false discovery rate (FDR) to adjust for multiple comparisons. The *P* for statistical significance was 0.006 (0.05/8) after the Bonferroni correction. We confirmed the proportional hazard assumption by including a time dependent exposure (time*acne) in the models (*P* for proportionality test > 0.05 for all tests). We used logistic regression models to calculate the odds ratios (ORs) and 95% CIs of melanoma in the melanoma case-control study²². We used the generalized linear models for the analyses of hormone levels and calculated the least square means of the steroid hormone levels by acne status²³. The variables adjusted in the models were presented in the footnotes of each table. Missing data were handled by a missing category if any. We conducted a sensitivity analysis restricting to the individuals without treatments for acne. All of the statistical analyses were carried out using Statistical Analysis System software (version 9.1.3; SAS Institute, Cary, NC). All *P* values were two-sided.

Results

We included 99,128 women in the analysis of severe teenage acne and cancer risk. During 20 years of follow-up from 1989 to 2009, 3,303 breast cancers, 397 melanomas, 347 thyroid cancers, 235 colorectal cancers, 165 non-Hodgkin lymphomas, 118 ovarian cancers, 115 cervical cancers and 109 endometrial cancers were diagnosed. Additionally, 6,577 BCC cases and 475 SCC cases were diagnosed. The distribution of basic characteristics of participants with and without history of severe teenage acne was similar (Table 1). There was a higher prevalence of prescription medications for acne treatment among those with severe teenage acne than those without (24.1 vs. 6.1% for antibiotics; 8.5 vs. 1.2% for tetracycline; and 13.0 vs. 1.1 % for oral Accutane). There was no substantial difference regarding the characteristics between women with and without information on teenage severe acne (Table S1).

In Table 2, we present the HRs and 95% CIs for each specific type of cancers. Among the individuals with a history of severe teenage acne, we identified an increased risk of breast cancer with crude HR of 1.23 (95% CI, 1.10-1.38; *P*=0.0005) and multivariable-adjusted HR of 1.17 (95% CI, 1.03-1.32; *P*=0.01), as well as an increased risk of melanoma with crude HR of 1.40 (95% CI, 1.02-1.92; *P*=0.04) and multivariable-adjusted HR of 1.44 (95% CI,

1.03-2.01; $P=0.03$). After the Bonferroni correction, the multivariable-adjusted associations became non-significant. The FDR for the multivariable-adjusted associations was 0.08 for breast cancer and 0.12 for melanoma. When we further restricted the analysis to individuals without acne medication, the risks remained similar to those in the overall analysis (1.18 vs. 1.17 for breast cancer; and 1.43 vs. 1.44 for melanoma). These associations were essentially unchanged in the analysis restricted to Caucasians (multivariable-adjusted HR: 1.16; 95% CI, 1.02-1.31 for breast cancer; and 1.49; 95% CI, 1.06-2.08 for melanoma). Previous studies have suggested the differential effects of BMI by menopausal status for breast cancer²⁴. Among postmenopausal women, the expected effects of BMI on breast cancer risk were opposite to that among premenopausal women. Thus, we modified the breast cancer models to allow for the differential effects by using a combined group for BMI and menopausal status. The results remained essentially unchanged. We further tested the interactions between acne history and other known/putative breast cancer risk factors and the P for interactions were 0.13-0.86 (Table S2). Besides, we detected the multivariable-adjusted HRs of 1.13 (95% CI: 0.77-1.65) for thyroid cancer, 1.07 (95% CI: 0.67-1.70) for colorectal cancer, 1.40 (95% CI: 0.74-2.65) for endometrial cancer, 1.04 (95% CI: 0.50-2.07) for cervical cancer, 0.69 (95% CI: 0.31-1.51) for ovarian cancer, and 0.46 (95% CI: 0.20-1.05) for non-Hodgkin lymphoma.

We confirmed the association between history of teenage acne and melanoma risk in an independent case-control study of 930 melanoma cases and 1,026 controls from the MD Anderson Cancer Center. The multivariable-adjusted OR for melanoma risk was 1.27 (95% CI, 1.03-1.56, Table 3). The P values for Goodness-of-Fit test were greater than 0.05 for all the models. The basic characteristics of participants with and without history of teenage acne are presented in Table S3. We additionally found that women with severe teenage acne were more likely to have moles compared with those without severe teenage acne in our cohort (52.7% vs. 50.1%; $P<0.001$). This association was replicated among the controls in the melanoma case-control study (55.2% vs. 45.1%; $P=0.004$). The multivariable-adjusted HRs for melanoma with and without adjustment for moles were not substantially different in our cohort (HR, 1.46, 95% CI, 1.05-2.04 without adjustment for moles v.s. HR, 1.44, 95% CI, 1.03-2.01 with adjustment). In the melanoma case-control study, the association between acne and melanoma was attenuated after adjusting for moles (OR, 1.42, 95% CI, 1.16-1.73 without adjustment for moles vs. OR, 1.27, 95% CI, 1.03-1.56 with adjustment). P for interaction between acne and moles on melanoma risk was 0.26. These findings were similar when we restricted the analysis to the individuals without treatments for acne.

To assess the potential confounders of melanoma risk, such as ultraviolet exposure and dermatology clinic visits, we analyzed the risk of non-melanoma skin cancers (including first-diagnosed SCC and BCC) by acne status. Individuals with severe teenage acne had a decreased risk of SCC (multivariable-adjusted HR, 0.47; 95% CI, 0.29-0.77; $P=0.003$). This association remained similar when we included SCC cases with history of BCC (multivariable-adjusted HR, 0.57; 95% CI, 0.37-0.87; $P=0.01$). No association was found for BCC risk (multivariable-adjusted HR, 1.05; 95% CI, 0.96-1.15; $P=0.26$).

Additionally, we found that women with history of severe teenage acne had higher mid-life plasma free testosterone levels compared to those without such a history among a subgroup

of our cohort population (0.17 vs. 0.16 ng/dL, $p=0.03$; Table S4). No difference was found for total testosterone or DHEAS.

Discussion

We suggested a history of teenage acne as a risk factor for melanoma by following 99,128 young women for 20 years in a large well-characterized cohort and validated this association in an independent U.S. melanoma case-control study of 930 cases and 1,026 controls. This association was independent from previously known melanoma risk factors. We additionally confirmed that women with history of severe teenage acne had elevated mid-life free testosterone levels, but the magnitude of the difference was small and the clinical significance requires further validation.

Acne has been suspected as a result of high levels of circulating androgens. Since 1980s, there has been cumulative evidence suggesting that women with acne have elevated androgen levels, especially free testosterone levels^{25; 26}. The possible link between androgens and melanoma has been speculated about for many years based on the phenomenon that men have a higher incidence of melanoma than women⁹. Experimental studies have also supported the role of sex hormones on growth of melanoma²⁷. A recent study reported that testosterone had effects on melanoma tumor growth in a dose-dependent manner in both *in vivo* and *in vitro* assays²⁸. However, previous studies reported inconsistent findings on the association between acne and melanoma risk based on small case-control study settings (with up to 452 melanoma cases)²⁹⁻³¹. Besides, the exact nature of the observed androgenic effect remains unclear. One of the mechanisms that we hypothesize is that androgens may affect melanoma risk through its influence on telomere length. It was reported that the androgen receptor interacts with telomeric proteins and has a role in telomere complex stability³². Melanocytes with longer telomere lengths experience a delayed entrance into senescence, which may lead to the increased formation of nevi and provide these cells with a greater opportunity to acquire additional mutations for the malignant transformation³³. Long telomeres have been associated with increased number of moles and increased risk of melanoma³⁴. Our findings that women with acne history had a higher level of circulating testosterone and an increased risk of melanoma support this hypothesis.

Of note, women with severe teenage acne did not have an increased risk of BCC or SCC, which are strongly associated with ultraviolet exposure, suggesting that the increased risk of melanoma was not likely to be confounded by excess ultraviolet exposure for acne treatment. However, SCC mainly reflects cumulative lifetime, not early life, exposures, and there might still be residual confounding. Besides, women with severe acne may also visit a dermatology clinic more often. However, the findings for BCC and SCC argue against detection bias. The inverse association between history of acne and SCC risk is worthy of further investigation. A previous study reported a highly protective role of endogenous estrogen against skin tumorigenesis by diverse agents in the mouse models of SCC³⁵. However, there is lack of evidence for the androgenic effect on SCC based on the published literatures.

Additionally, our study suggested that women with a history of severe teenage acne had an increased risk of breast cancer. However, this finding became non-significant after adjusting for multiple tests. Even though, prospective cohort studies has suggested that high levels of pre-diagnostic circulating androgens are associated with increased risk of breast cancer³⁶. A prospective nested case-control study of breast cancer within the NHSII cohort has found a positive association between plasma testosterone levels and breast cancer risk¹⁸. Such an association remained essentially unchanged after adjustment for estradiol, suggesting that the association with androgens is at least partly independent of estrogen.

Of interest, we most recently found that women with more cutaneous nevi had higher risks of breast cancer compared to women with no nevi by following 74,523 female nurses for 24 years (1986-2010) in the Nurses' Health Study³⁷. The multivariable-adjusted HR was 1.04 (95% CI, 0.98-1.10) for 1-5 nevi, 1.15 (95% CI, 1.00-1.31) for 6-14 nevi, and 1.35 (95% CI, 1.04-1.74) for 15 or more nevi (*P* for continuous trend=0.003). Women with 6 or more nevi had 45.5% higher level of free estradiol and 47.4% higher level of free testosterone compared to those with no nevus (*P* for trend=0.001 for both), which was consistent with and supported the present study.

Of note, polycystic ovary syndrome, the most common cause of elevated androgen levels in women, has acne as one of its main symptoms. These women have higher infertility rates that could explain a higher breast cancer risk due to no or children conceived at a later age. However, the parity and age at first birth appear similar comparing women with and without acne in our study population, suggesting these factors are unlikely to confound our finding on breast cancer.

Another interesting finding was an inverse association between acne and non-Hodgkin lymphoma. Previous study found hyper-methylation of the androgen receptor gene in follicular non-Hodgkin's lymphomas, suggesting a suppressed androgenic effect in non-Hodgkin's lymphoma³⁸. Given that acne is generally linked to an overexpression of androgen, our finding was consistent with the previous report, although the association was not strictly statistical significant. Further studies are needed to verify the inverse association between androgen and non-Hodgkin's lymphoma.

Our findings were based on a large prospective cohort study and we were able to thoroughly adjust for the previously identified cancer risk factors. We further confirmed teenage acne as a surrogate for mid-life androgen levels to predict subsequent cancer risk. Although a single plasma hormone measurement provides a reasonable measure of levels over a several-year period, most androgenic activity in women originates from the peripheral conversion of precursors such as DHEA into androgens within the cells of target tissues, and this activity cannot be detected by measuring circulating androgens³⁹. Additionally, women with acne have enhanced dermal sensitivity to androgens and breast tissue is embryologically closely related to accessory skin structures⁴⁰, so the presence of acne may reflect end-organ response to hormones. One limitation of this study is that we used self-reported information on acne and moles, and no standard was specified for acne severity in the questionnaire. However, the high education level and interest in health of cohort members allows high quality and valid information to be collected on self-administered forms. In addition, a

previous study demonstrated that people reporting acne of some severity were likely to have seen a physician⁴¹ and the majority of studies on mole counts have shown a substantial agreement between self-counts and dermatologist counts⁴². Besides, we did not collect information on moderate teenage acne. Hence we were not able to evaluate the dose-response relationship. We did not collect information on the type of moles or on the number of moles on other body parts besides the lower legs, which may lead to a possibility of residual confounding. However, examining the limbs only was suggested to be a practical and suitable tool for predicting total nevus count based on a previous study⁴³. The self-reported mole counts in our cohort predict melanoma risk⁴⁴, and our genome-wide association study on self-reported mole count in our cohort confirmed previously identified loci in nevo-genesis⁴⁵.

In summary, we identify a history of teenage acne as a novel risk factor for melanoma independent of the previously identified risk factors. A history of teenage acne may be an early-stage marker of high androgen levels and might have potential importance to help identify populations at higher cancer risk. Our findings support a need for continued investigation of the relationship between acne and hormone-related cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

We identify a history of teenage acne as a novel risk factor for melanoma independent from the previously identified risk factors. Our findings may provide a novel insight into the etiology of melanoma. Additionally, a history of acne may be an early-stage marker of high androgen levels, which might have potential importance to help identify populations at higher risk of hormone-related cancers.

Table 1Baseline characteristics of women according to history of severe teenage acne in the NHSII cohort¹.

Characteristics	Severe teenage acne	
	No (n=91,202)	Yes (n=7,926)
Mean age, years (SD)	34.3(4.7)	34.2(4.6)
Caucasians, %	93.0	93.3
Height, m (SD)	1.6(0.1)	1.6(0.1)
Body mass index, kg/m ² (SD)	24.1(5.0)	24.1(5.0)
Body mass index at age 18, kg/m ² (SD)	21.3(3.4)	21.2(3.2)
Alcohol consumption at 1991, gm/day (SD)	3.1(6.0)	3.0(5.9)
Physical activity, met-h/week (SD)	28.7(70.0)	26.7(64.0)
Multi-vitamin use, %	45.3	48.9
Current smoker, %	13.3	12.2
History of benign breast disease, %	9.8	11.3
Family history of breast cancer, %	5.9	6.2
Current use of oral contraceptive, %	13.3	13.1
Postmenopausal women, %	5.7	6.6
Age at menarche, years (SD)	13.4(1.4)	13.3(1.5)
Parity among parous women, times (SD)	1.4(1.2)	1.3(1.2)
Age at first birth, years (SD)	25.4(4.0)	25.6(4.1)
Red hair color, %	3.9	3.1
Number of severe sunburns at ages 15-20, 5+, %	9.5	10.7
Childhood tendency to severe blistering sunburns, %	6.9	8.2
Presence of moles on lower legs, %	50.1	52.7
Family history of melanoma, %	4.2	5.0
Antibiotics use for acne treatment, %	6.1	24.1
Duration of tetracycline use, 5 years +, %	1.2	8.5
Oral Accutane use, %	1.1	13.0

¹Based on information collected in the 1989 questionnaire unless specified.

Table 2

History of severe teenage acne and risk of cancers in the NHSII cohort.

Cancers	Cases	Age-adjusted HR	Multivariable-adjusted HR ¹
Breast cancer	3,303	1.23(1.10-1.38)	1.17(1.03-1.32) ²
Melanoma	397	1.40(1.02-1.92)	1.44(1.03-2.01) ³
Thyroid cancer	347	1.17(0.81-1.68)	1.13(0.77-1.65)
Colorectal cancer	235	1.15(0.73-1.79)	1.07(0.67-1.70)
Non-Hodgkin lymphoma	165	0.44(0.19-0.98)	0.46(0.20-1.05)
Ovarian Cancer	118	0.73(0.34-1.56)	0.69(0.31-1.51)
Cervical cancer	115	1.09(0.57-2.08)	1.04(0.52-2.07)
Endometrial cancer	109	1.32(0.70-2.45)	1.40(0.74-2.65)

¹ Adjusted for age, ancestry, body mass index, alcohol consumption, physical activity, multi-vitamin use, smoking status, oral contraceptive use, menopausal status and use of hormone replacement, medications for acne treatment including the use of tetracycline, oral Accutane and antibiotics;

² Additionally adjusted for history of benign breast disease, family history of breast cancer, age at first birth and parity, age at menarche, height and body mass index at age 18;

³ Additionally adjusted for natural hair color, childhood tendency to sunburn, number of sunburns at ages 15-20, family history of melanoma and self-reported mole count on lower legs, history of squamous cell carcinoma and basal cell carcinoma.

Table 3

History of teenage acne and melanoma risk in the melanoma case-control study from the MD Anderson Cancer Center.

Melanoma	Teenage acne	
	No (n=1,328)	Yes (n=628)
Cases (%), n=930	588 (63.2)	342 (36.8)
Controls (%), n=1,026	740 (72.1)	286 (27.9)
Odds ratio (95% confidence interval)		
Age- and gender-adjusted	1.00 (Ref)	1.50(1.23-1.82)
Multivariable-adjusted ¹	1.00 (Ref)	1.42(1.16-1.73)
Multivariable-adjusted ²	1.00 (Ref)	1.27(1.03-1.56)

¹ Adjusted for hair color, eye color, skin color, freckling when out in the sun, severe blistering sunburns before age 16, and tendency to tan after exposure to the sun for 30-40 minutes;

² Additionally adjusted for the presence of moles.